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(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : CONROW, Raymond, E. [US/US]; 3612 Woodmoor Road, Fort Worth, TX 76133 (US). CLARK, Abbot, F. [US/US]; 5708 Stage Line Drive, Arlington, TX 76017 (US).

(74) Agents: RYAN, Patrick et al.; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134 (US).

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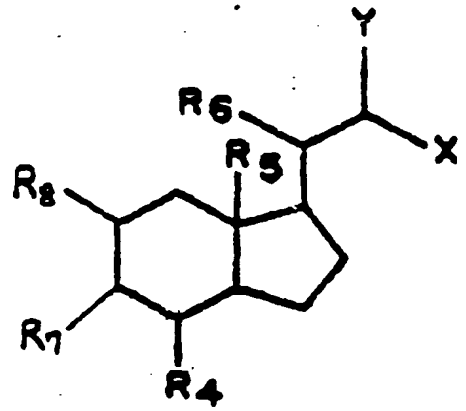

(I)

(57) Abstract

Substituted hydrindanes, particularly of formula (I) in which X, Y, R_4, R_5, R_6, R_7 and R_8 are as defined in the description, and their use in controlling angiogenesis dependent diseases in warm blooded animals, as well as a method for preparing 3-bromo-(2,2-dimethyl)propyl benzoate are disclosed.

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SUBSTITUTED HYDRINDANES FOR THE TREATMENT OF ANGIOGENESIS-DEPENDENT DISEASES

Background of the Invention

Field of Invention

This invention is directed to substituted hydrindanes and their use in preventing and treating angiogenesis-dependent diseases in warm blooded animals.

Description of Related Art

Angiogenesis refers to the generation and growth of new blood vessels and is often referred to as neovascularization. A number of compounds have been shown to inhibit angiogenesis. PF4 and its derivatives (Maione, et al., "Inhibition of angiogenesis by recombinant human platelet factor-4 and related peptides," Science, 247:77-79, 5 January 1990), inhibitors of collagen synthesis (Ingber & Folkman, "Inhibition of Angiogenesis through modulation of collagen metabolism," Laboratory Investigation, 59:44-51, 1988), synthetic analogs of fumagillin (Ingber, et al., "Synthetic analogues of fumagillin that inhibit angiogenesis and suppress tumor growth," Nature, Vol. 348:555-557, 6 Dec. 1990), retinoids (Oikawa, et al., "A highly potent antiangiogenic activity of retinoids," Cancer Letters, 48:157-162, 1989), herbimycin A (Oikawa, et al., "Powerful antiangiogenic activity of herbimycin A," The Journal of Antibiotics, XLII:1202-1204, July, 1989), vitamin D analogs including calcitriol (Oikawa, et al, "Inhibition of angiogenesis by vitamin D_3 analogues," European J. Pharmacology, 178:247-250, 1990), and angiostatic steroids in the presence of a heparin cofactor (Crum, et al., "A new class of steroids which inhibits angiogenesis in the presence of heparin or a heparin fragment," Science, 230:375-378, 20 December 1985) have been demonstrated to inhibit angiogenesis in the chick embryo chorioallantoic membrane (CAM) model of neovascularization. Topical ocular administration of angiostatic steroids in a cyclodextrin formulation inhibits lipopolysaccharide induced corneal neovascularization in the rabbit (Li, et al., "Angiostatic steroids potentiated by

sulphated cyclodextrin inhibit corneal neovascularization," Investigative Ophthalmology and Visual Science, 32:2898-2905, October, 1991).

Summary of Invention

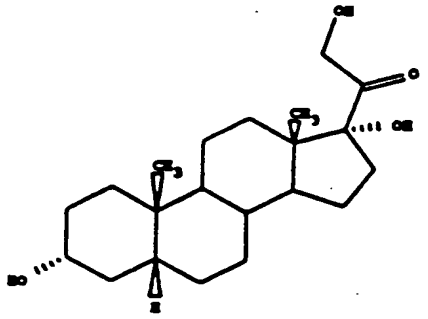
This invention is directed to substituted hydrindanes useful in the inhibition of neovascularization. These compounds can be used in the treatment of angiogenesis-dependent diseases. These compounds are particularly useful for the treatment and control of angiogenesis associated with ocular neovascular diseases, solid tumor growth, diabetes and arthritis.

This invention is also directed to methods for controlling and preventing angiogenesis dependent diseases through the systemic or local administration of the compositions herein disclosed.

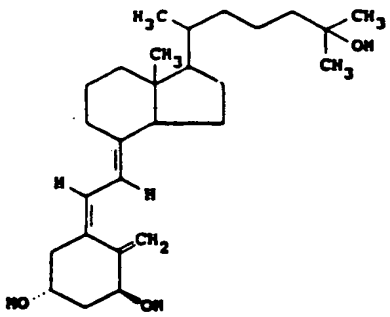
Detailed Description of Preferred Embodiments

The development and formation of new blood vessels for the purpose of sustaining vital tissue is known as angiogenesis or neovascularization. Angiogenesis is a very important process in the development of an organism; however, a large number of diseases are associated with the aberrant growth of new blood vessels. These diseases are referred to as angiogenesis dependent diseases. The substituted hydrindanes of the present invention are useful in preventing and treating, collectively referred to herein as "controlling," neovascularization associated with disease in warm blooded animals, including humans.

Two classes of compounds which are known to inhibit angiogenesis in the chick embryo chorioallantoic membrane (CAM) model of neovascularization are angiostatic steroids, such as tetrahydrocortexolone, and dihydroxy-vitamin D analogs, such as calcitriol. Vitamin D is a steroid in which the B ring of the steroid nucleus is photochemically cleaved (i.e. a B-seco steroid).



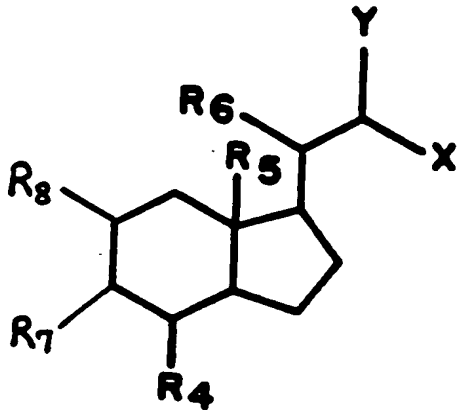
Tetrahydrocortexolone (THS)



Calcitriol

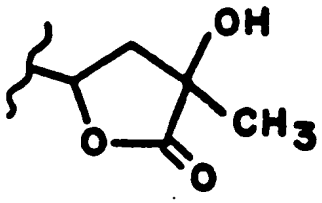
Our structure-activity relationship studies of angiostatic steroids and vitamin D analogs in the chick CAM model of neovascularization allowed us to predict that certain fragments of angiostatic steroids or vitamin D analogs would be angiostatic (i.e. inhibit neovascularization). Compounds lacking the A and B rings of the steroid nucleus and containing the six carbon C ring and the five carbon D ring (i.e. substituted hydrindanes) were prepared and evaluated for angiostatic activity in the chick CAM model (details of the methods of the CAM assay may be found in McNatt, et al., Angiostatic activity and metabolism of cortisol in the chorioallantoic membrane (CAM) of the chick embryo J. Steroid Biochem. Molec. Biol. Vol. 42:687-693, 1992). These substituted hydrindanes had angiostatic activity 1000-10,000 times as potent as angiostatic steroids tested in this system.

The substituted hydrindanes of the present invention have the following formula:



1

where X is OH, OR_1, OR_2, $OS(O)_2R_3$, $ON=CHR_1$, $ON=CR_1R_1$, CN, R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_1$, $C(OR_1)R_1R_1$, $C(OR_2)R_1R_1$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, $S(=O)_nH$, $S(=O)_nR_1$, SR_2, $P(=O)R_1R_1$, $P(=O)(OH)_2$, $P(=O)(OH)(OR_1)$, $P(=O)(OR_1)(OR_1)$, $P(=O)(OH)(NH_2)$, $P(=O)(OR_1)(NH_2)$, $P(=O)(OH)(NHR_1)$, $P(=O)(OH)(NR_1R_1)$, $P(=O)(OR_1)(NHR_1)$ $P(=O)(OR_1)(NR_1R_1)$, NH_2, NHR_1, NHR_2, NR_1R_1, NR_1R_2, NHOH, $N(OH)R_1$, $N(OH)R_2$, $NH(OR_1)$, $NH(OR_2)$, $N(OR_1)R_2$, $N(OR_2)R_1$, $N(OR_2)R_2$, $N(OR_1)R_1$, $^{\oplus}S(R_1)(R_1)$ $Q^{\ominus}$, $^{\oplus}N(R_1)(R_1)(R_1)$ $Q^{\ominus}$ wherein $Q^{\ominus}$ is a halide, sulfonate, or carboxylate anion; $C(=O)R_1$, $C(=O)R_2$, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$, $C(=O)N(OH)R_1$, $C(=O)N(OR_1)R_1$, $C(=O)N(OR_2)R_1$; or



n = 0, 1 or 2;

R_1 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR_3, or 6 OR_2; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl,

isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C_1 - C_6 alkyl groups;

R_2 is C(=O)H, $C(=O)R_1$, $C(=0)OR_1$, C(=0)OH, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$;

R_3 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

R_4 is H, (=O), OR_2, OR_1, OH, =NOH, $=NOR_1$, $=NOR_2$;

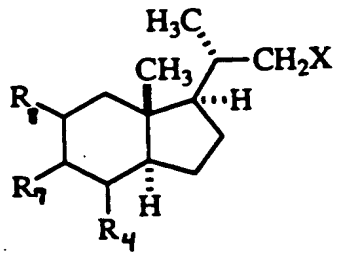
R_5 and R_6 are independently H, CH_3 or CH_2CH_3;

Y is H, OH, OR_1, OR_2 or (=0), with the proviso that if Y is OH, then X is R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, and if Y is (=O) then X is R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, NH_2, NHR_1, NR_1R_1, NHOH, $N(OH)R_1$, $NH(OR_1)$, $NH(OR_2)_2$, $N(OR_1)R_1$, or $N(OR_2)R_1$; and

R_7 and R_8 are independently H or C_1 to C_6 alkyl, branched alkyl, hydroxyalkyl, optionally unsaturated; or R_7 and R_8 together form a double bond.

Unless otherwise specified, all substituent groups can be attached to the hydrindane ring system in either the alpha or beta position. Additionally, the above structures include all pharmaceutically acceptable salts and esters of the substituted hydrindanes.

Compounds of Formula 1 having the following structure are preferred (Formula 2):



2

where X is $C(OH)R_1R_1$, $C(OR_1)R_1R_1$, $C(OR_2)R_1R_1$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, $S(=O)_nH$, $S(=O)_nR_1$, SR_2, $P(=O)R_1R_1$, $P(=O)(OH)_2$, $P(=O)(OH)(OR_1)$, $P(=O)(OR_1)(OR_1)$, $P(=O)(OH)(NH_2)$, $P(=O)(OR_1)(NH_2)$, $P(=O)(OH)(NHR_1)$, $P(=O)(OH)(NR_1R_1)$, $P(=O)(OR_1)(NHR_1)$ $P(=O)(OR_1)(NR_1R_1)$, NH_2, NHR_1, NHR_2, NR_1R_1, NR_1R_2, NHOH, $N(OH)R_1$, $N(OH)R_2$, $NH(OR_1)$, $NH(OR_2)$, $N(OR_1)R_2$, $N(OR_2)R_1$, $N(OR_2)R_2$, $N(OR_1)R_1$, $^{\oplus}S(R_1)(R_1)$ $Q^{\ominus}$, $^{\oplus}N(R_1)(R_1)(R_1)$ $Q^{\ominus}$ wherein $Q^{\ominus}$ is a halide, sulfonate, or carboxylate anion; $C(=0)R_1$, $C(=0)R_2$, $C(=0)NH_2$, $C(=0)NHR_1$, $C(=0)NR_1R_1$, $C(=0)N(OH)R_1$, $C(=0)N(OR_1)R_1$, $C(=0)N(OR_2)R_1$;

n = 0, 1 or 2;

R_1 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR_3, or 6 OR_2; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C_1 - C_6 alkyl groups;

R_2 is C(=O)H, $C(=O)R_1$, $C(=0)OR_1$, C(=0)OH, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$;

R_3 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

R_4 is H, OR_2, OR_1, OH, =NOH, $=NOR_1$, $=NOR_2$; and provided that if X is $S(O)_2$(optionally substitued phenyl) then $R_4 \neq$ OH, or (=O); and

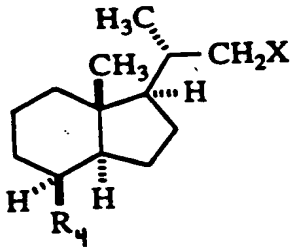
R_7 and R_8 are H or together are optionally a double bond;

and wherein aryl denotes phenyl, naphthyl, furyl, thienyl, pyridyl, benzofuryl, indolyl, benzothienyl, quinolyl or isoquinolyl;

R_1R_1 attached to the same C, S, P or N atom can form a ring of from 3 through 7 members; and

for those substituents containing more than one R_1, R_2, or R_3, each R_1, R_2, or R_3 may be the same or different.

More preferred compounds are compounds of Formula **2** where the stereochemistry is as specified below.



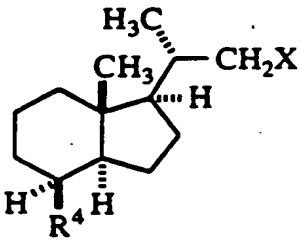
where X and R_4 are the same as above.

Especially preferred are De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, De-*A,B*-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, and De-*A,B*-23-thiacholestan-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate.

The compounds of Formula **2** can be prepared from diol **3a**. Stereoisomers of compounds of Formula **2**, as well as related compounds of Formula **1** having substituents $R_5 \neq CH_3$ and $R_6 \neq CH_3$, can be prepared by total synthesis using appropriately modified materials and procedures, and/or in some cases from materials (e.g. Compound **3a**) derived from Vitamin D_2, at the discretion of one skilled in the art.

The compounds of Formula **2** can be prepared starting with the known "Inhoffen-Lythgoe diol" **3a** which can be prepared from Vitamin D_2. Alternatively, **3a** can be prepared by total synthesis, for example, as described in: P.M. Wovkulich et al., Tetrahedron *40*, 2283 (1984), or in: W.S. Johnson et al., J. Am. Chem. Soc. *106*, 1138 (1984).

Conversion of the primary hydroxyl group of diol **3a** to a good leaving group, as in the known monotosylate **3b**, allows the preparation of thioether and amine derivatives of hydrindanes. For example, reaction of **3b** with benzyl mercaptan and a base produces benzyl thioether **3c**. Compound **3c** can be treated with an



3a, R^4 = OH, X = OH
3b, R^4 = OH, X = OTs
3c, R^4 = OH, X = SCH_2Ph
3d, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = SCH_2Ph
3e, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = $S(O)_2CH_2Ph$
3f, R^4 = OH, X = SH
3g, R^4 = OH, X = $SCH_2C(CH_3)_2OH$
3h, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = OTs
3j, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = SH
3k, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = $SCH_2C(CH_3)_2CH_2OC(=O)Ph$
3m, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = $S(O)_2CH_2C(CH_3)_2CH_2OC(=O)Ph$
3n, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = S-(2-(5-methyl-1,3,4-thiadiazolyl))
3p, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = $N^+(CH_3)_2CH_2CH_2OH$, OTs^-
3q, R^4 = $OC(=O)NHC_6H_4Br$-*p*, X = $NHCH_2C(CH_3)_2CH_2OH$
3r, R^4 = OH, X = CN
3s, R^4 = OH, X = COOH
3t, R^4 = OH, X = $C(=O)N(CH_3)OCH_3$
3u, R^4 = OH, X = $C(=O)NHCH_2C(CH_3)_2CH_2OH$
3v, R^4 = $OC(CH_3)_3$, X = OTs
3w, R^4 = $OC(CH_3)_3$, X = I
3x, R^4 = $OC(CH_3)_3$, X = $P(O)(O\text{-}i\text{-}Pr)_2$
3y, R^4 = OCH_2Ph, X = CHO
3z, R^4 = OCH_2Ph, X = $C(=O)CH_2C(CH_3)_2OH$

appropriate acylating agent, such as 4-bromophenyl isocyanate to produce thioether carbamate **3d**. Reaction of a thioether such as **3d** with an oxidant, for example, 3-chloroperoxybenzoic acid, yields a sulfone, e.g. **3e**, or the corresponding sulfoxide.

Alternatively, hydrindane thioethers can be formed by reacting a hydrindane thiol, e.g. **3f**, with an alkylating agent. For example, use of such as isobutylene oxide, gives thioether **3g**. Thiol **3f** can be prepared via cleavage of benzyl thioether **3c**, using, for example, sodium in liquid ammonia.

Tosylate **3b** can be treated with an appropriate acylating agent, such as 4-bromophenyl isocyanate to produce the tosyloxy carbamate **3h**. Displacement of the tosyl group of **3h** with a thiolcarboxylate salt, such as potassium thiolacetate, followed by cleavage of the acetyl group, provides thiol carbamate **3j**.

Thiol carbamate **3j** can be alkylated on sulfur to provide various hydrindane thioethers. For example, treatment of **3j** with 3-bromo-(2,2-dimethyl)propyl benzoate (prepared from 5,5-dimethyl-2-phenyl-1,3-dioxane according to the method of Hanessian, (Org. Synth. *65*, 243) and potassium *tert*-butoxide in dimethyl sulfoxide solution yields thioether **3k**, which can be oxidized as above to sulfone **3m**, or the corresponding sulfoxide.

Reaction of tosylate **3h** with a heterocyclic thiol, e.g., 2-mercapto-5-methyl-1,3,4-thiadiazole, produces heterocyclic thioethers of hydrindanes, such as **3n**.

Hydrindane quaternary ammonium salts, such as **3p**, can be made by reacting tosylate **3h** with a tertiary amine, in this case 2-(N,N-dimethylamino)ethanol. Use of a primary amine leads instead to secondary amino compounds, e.g., **3q**.

Hydrolysis of the known nitrile **3r** (prepared from tosylate **3b**: P.M. Wovkulich et al., cited above) provides carboxylic acid **3s**, which can be converted into hydrindane amides such as **3t** and **3u** by treatment with an amine such as N,O-dimethylhydroxylamine or 3-amino-2,2-dimethylpropanol, respectively, in the presence of a coupling reagent, for example, a 1,3-dialkyl carbodiimide such as 1-ethyl-3-(dimethylaminopropyl) carbodiimide hydrochloride.

Hydrindane phosphonic acid derivatives, e.g., **3x**, can be prepared from primary halo compounds such as iodide **3w**, using Arbusov reaction conditions such as those described by Karanewsky et al., J. Med. Chem, *33*, 2952 (1990); this

reference also teaches methods for converting dialkyl phosphonates to other phosphorus compounds such as monoalkyl phosphonates, phosphinates and phosphonamides.

Hydrindane ketones, *e.g.*, **3z**, can be prepared in a variety of ways. For example, reaction of known hydrindane aldehyde **3y** (Johnson, et al., cited above) with an organometallic reagent, for example, that derived from isobutylene oxide by the method of T. Cohen et al., J. Org. Chem. *55*, 1528 (1990), followed by oxidation of the intermediate secondary alcohols with, e.g., a chromium (VI) reagent, provides ketone **3z**. Other methods of preparing ketones are well known in the art, for example, reaction of organolithium reagents with N-alkoxy-N-alkyl amides such as **3t**, or with acids such as **3s**.

Without being bound by any theory, it is believed that angiostatic agents work by inhibiting one or more steps in the process of neovascularization, regardless of the cause; therefore the angiostatic substituted hydrindanes of this invention are useful in the treatment and prevention of neovascularization associated with a variety of diseases and surgical complications. The formation of new blood vessels (i.e. angiogenesis) is a natural developmental process; however, once a tissue has formed, there is generally no need for additional new blood vessels. A number of diseases are characterized by the growth of new blood vessels, and these diseases can be effectively treated through the inhibition of neovascularization (Doctrow & Kulakowski, "Angiogenesis modulators - New drugs for controlling blood vessel growth?," Drug News & Perspectives 2:74-81, March 1989; Maione & Sharpe, "Development of angiogenesis inhibitors for clinical applications," Trends in Pharmaceutical Sciences, 11:457-461, November 1990). Many different substances have been found to induce and promote neovascularization (Folkman, et al., "Angiogenic factors," Science 235:442-447, 1987; BenEzra, "Neovasculogenic ability of prostaglandins, growth factors and synthetic chemoattractants," American J. Ophthalmology, 86:445-461, October 1978). Inhibition may differ in the various neovascular diseases; however, it is believed that once initiated, the basic process of neovascularization is similar in all tissues regardless of the associated disease (Furcht, "Critical factors controlling angiogenesis: cell products, cell matrix and growth factors," Laboratory Investigation, 55:505-509, 1986).

The substituted hydrindanes of the present invention can be used in treating neovascularization associated with, for example: cancer, solid tumors, arthritis, diabetes, arteriosclerosis, angiofibroma, arteriovenous malformations, corneal graft neovascularization, delayed wound healing, diabetic retinopathy, age related macular degeneration, granulations, burns, hemangioma, hemophilic joints, hypertrophic scars, neovascular glaucoma, nonunion fractures, Osler-Weber Syndrome, psoriasis, pyogenic granuloma, retrolental fibroplasia, pterigium, scleroderma, trachoma, vascular adhesions, ocular neovascularization, parasitic diseases, hypertrophy following surgery, inhibition of hair growth, inhibition of ovulation and corpus luteum formation and inhibition of embryo implantation and development in the uterus.

In particular, these compounds are useful in preventing and treating any ocular neovascularization, including, but not limited to: retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy, age related macular degeneration); rubeosis iritis; inflammatory diseases; chronic uveitis; neoplasms (retinoblastoma, pseudoglioma); Fuchs' heterochromic iridocyclitis; neovascular glaucoma; corneal neovascularization (inflammatory, transplantation, developmental hypoplasia of the iris); neovascularization resulting following combined vitrectomy and lensectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis, carotid artery ischemia); pterigium; neovascularization of the optic nerve; and neovascularization due to penetration of the eye or contusive ocular injury.

The substituted hydrindanes of the present invention can be incorporated into various formulations for delivery. The type of formulation (topical or systemic) will depend on the site of disease and its severity. These compounds can be systemically delivered orally in a tablet or capsule form or by parenteral injection. The compounds can be formulated into gels, ointments, or creams for topical administration to the skin. For administration to the eye, topical formulations can be used and can include ophthalmically acceptable preservatives, surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic

ointment formulations, an angiostatic substituted hydrindane is combined with a preservative in an appropriate vehicle, such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations comprising the angiostatic substituted hydrindanes of the present invention can be prepared by suspending an angiostatic hydrindane in a hydrophilic base prepared from a combination of, for example, Carbopol® 940 (a carboxy vinyl polymer available from BF Goodrich Company), according to published formulations for analogous ophthalmic preparations. Preservatives and antimicrobial agents can also be incorporated in such gel formulations. Angiostatic substituted hydrindanes can also be formulated for sterile ophthalmic intraocular injections. Systemic formulations for treating ocular neovascularization can also be used, for example, orally ingested tablets and parenteral injections.

The specific type of formulation selected will depend on various factors, such as the angiostatic substituted hydrindane (or its salt or ester) being used, the dosage frequency and the severity and the location of the disease. For ocular neovascular diseases, topical ophthalmic aqueous solutions, suspensions, ointments and gels are the preferred dosage forms for the treatment of neovascularization of the front of the eye (e.g. the cornea, iris, trabecular meshwork) or the back of the eye if the angiostatic agent can be formulated such that it can be delivered topically and penetrate the tissues of the front of the eye to get to the back of the eye. The angiostatic agent will normally be contained in these formulations in an amount from about 0.0001 to 1 weight percent. For topical ocular administration, these formulations are delivered to the surface of the eye one to six times a day, depending on the discretion of the skilled clinician. Systemic administration, for example in the form of tablets, is particularly useful in the treatment of neovascularization of the back of the eye, such as the retina. Tablets containing 1-2000 mg of the angiostatic agent can be taken 1-4 times per day depending on the discretion of the skilled clinician.

The substituted hydrindanes of this invention are also useful in controlling intraocular pressure associated with primary open angle glaucoma (POAG) and in

controlling the rise in intraocular pressure sometimes associated with the use of glucocorticoids.

The formulations set forth in the following examples for topical ocular suspensions, intraocular injections, and oral tablets can be prepared according to procedures known to those skilled in the art of formulating drugs.

Example 1: Topical Ocular Suspension

	Amount (wt%)
Substituted hydrindane	0.001-1.0
Tyloxapol	0.01 to 0.05
HPMC	0.5
Benzalkonium chloride	0.01
Sodium Chloride	0.8
Edetate disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified water	q.s. 100 ml

Example 2: Formulation for Sterile Intraocular Injection

Each mL contains:	
Substituted hydrindane	0.01-10.0 mg
Sodium chloride	7.14 mg
Potassium chloride	0.38 mg
Calcium chloride dihydrate	0.154 mg
Magnesium chloride dihydrate	0.20 mg
Dried sodium phosphate	0.42 mg
Sodium bicarbonate	2.1 mg
Dextrose	0.92 mg
NaOH/HCl	q.s. pH 7.2
Purified water for injection	q.s. 1 mL

Example 3: Formulation for Tablet

1-2000 mg of substituted hydrindane with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formation.

Examples 4-6: Angiostatic Activity for 3 Classes of Compounds

Angiostatic activity of the test compounds was evaluated in the chicken embryo chorioallantoic membrane (CAM) model of neovascularization as described by McNatt et al. Briefly, 1.0 ng of the indicated substituted hydrindane was added to a 10 µL bead containing 1% agarose and liposomes (2.5% dimyristoyl phosphatidyl choline) and placed on the CAM of a shell-less, 5-6 day chick embryo. After an additional 2 days of incubation at 37°C, the zone of avascularity surrounding the dose bead was evaluated. Angiostatic activity is expressed as the angiostatic response frequency per nmole of test compound.

Example	Compound Class	Class Representative Evaluated	Angiostatic Factor (Response Frequency/nmole)
4	Angiostatic steroid	Tetrahydrocortisol	2
5	Vitamin D analogs	Calcitriol	23,000
6	Substituted hydrindanes	De-*A*,*B*-cholestan-8β,23S,25R,26-tetrol	33,000

Examples 7-23: Angiostatic Activity of Substituted Hydrindanes Evaluated in Chick Embryo Model of Neovascularization

A number of compounds of Formula II were prepared and evaluated in the CAM model as in Examples 4-6 above. Angiostatic activity results for these compounds are shown in the table below. Angiostatic activity is expressed as the angiostatic response frequency per nmole of test compound relative to positive and negative controls.

EXAMPLE	COMPOUND	R.A.F.*
7.	De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate	3.14
8.	De-*A,B*-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate	2.91
9.	De-*A,B*-23-thiacholestan-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate	2.80
10.	De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate	2.18
11.	De-*A,B*-23,24-dinor-22-(carbethoxymethyl)thiocholan-8β-ol-(4-bromophenyl) carbamate	1.97
12.	De-*A,B*-23,24-dinor-22-(2-(1-methylimidazolyl)thio)-cholan-8β-ol-(4-bromophenyl) carbamate	1.83
13.	De-*A,B*-23-thiacholestan-8β,25-diol-8β,25-bis (4-bromophenyl) carbamate	1.75
14.	De-*A,B*-23,24-dinor-22-(2-(5-methyl-1,3,4-thiadiazolyl) thio)-cholan-8β-ol-(4-bromophenyl) carbamate	1.67
15.	De-*A,B*-23-thiacholestan-8β,25-diol-23-dioxide-8β-(4-bromophenyl) carbamate	1.57
16.	De-*A,B*-cholestan-8β,23R,25S,26-tetrol	1.54
17.	De-*A,B*-23,24-dinorcholan-8β,22-diol-bis(phenyl carbamate)	1.25
18.	De-*A,B*-cholestan-8β,23S,25R,26- tetrol	1.00
19.	De-*A,B*-cholest-25-en-8β,23S-diol	0.85
20.	De-*A,B*-23,24-dinor-8β-hydroxycholan-22-(N-methyl-N-methoxy) carboxamide	0.82
21.	De-*A,B*-23,24-dinor-8β-hydroxycholan-22-(N-(2,2-dimethyl-3-hydroxy)propyl) carboxamide	0.49
22.	De-*A,B*-23,24-dinorcholan-8β,22-diol	0.39
23.	De-*A,B*-23,24-dinor-8β-hydroxycholan-22-carboxylic acid	0.37

* = relative angiostatic factor (angiostatic activity at 1 ng relative to De-*A,B*-cholestan-8β,23S,25R,26-tetrol)

Examples 24-42: Preparation of Substituted Hydrindanes

Example 24:

De-*A,B*-23,24-dinor-24-phenyl-23-thiacholan-8β-ol (**3c**).

Benzyl mercaptan (15 mL) was added in 2-mL portions to a stirred suspension of 5.4 g of NaH (60%, oil dispersion) in 200 mL of dry DMF under Ar, keeping T<35°C. After evolution of H_2 ceased, the solution was cooled to 10 °C and a solution of tosylate **3b** in 80 mL of dry DMF was added in 4 portions. The solution was stirred (to 24°C) for 15 h, then quenched carefully with water. The mixture was poured into 1L of water and extracted with ether and ethyl acetate. The combined organic extracts were washed with 1M NaOH (twice), water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica (10%-25% EtOAc-hexane) to give 27.7 g of an oil.

NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.02 (d, 3H), 1.1-2.0 (m, 14H), 2.35 (ABX, 2H), 3.68 (s, 2H), 4.05 (br s, 1H), 7.3 (br s, 5H).

Example 25:

De-*A,B*-24-phenyl-23-thiacholan-8β-ol-8β-(4-bromophenyl) carbamate (**3d**).

4-Bromophenyl isocyanate (3.07 g) was added to a stirred solution of De-*A,B*-23,24-dinor-24-phenyl-23-thiacholan-8β-ol (**3c**, 3.79 g) in 24 mL of dry pyridine under Ar. After 68 h, water (5mL) was added and the mixture was stirred for 20 min. The mixture was diluted with ether and washed with water, 1M HCl (to pH 1), water (to pH7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was suspended in 1:3 EtOAc-hexane, eluted through a silica pad and the eluate concentrated to give 5.88 g of a foam.

NMR ($CDCl_3$): δ 0.85 (s, 3H), 1.03 (d, 3H), 1.0-2.0 (m, 13 H), 2.35 (ABX, 2H), 3.68 (s, 2H), 5.14 (br s, 1H), 6.48 (br s, 1H),
7.3 (br s, 5H), 7.35 (AB, 4H).

Example 26:

De-*A,B*-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate (**3e**).

3-Chloroperoxybenzoic acid (1.98 g) was added in portions to a stirred solution of De-*A,B*-24-phenyl-23-thiacholan-8β-ol-8β-(4-bromophenyl) carbamate (**3d**, 1.97 g) in 15 mL of CH_2Cl_2. After 15 h, the mixture was diluted with EtOAc and washed with 1M NaOH (twice), water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was triturated (5% ether-hexane) to give 1.89 g of a pink solid, m.p. 78-84 °C.

Anal. Calc'd:	C, 59.12;	H, 6.25;	N, 2.55;	S, 5.85.
Found:	C, 59.02;	H, 6.28;	N, 2.52;	S, 5.82.

Example 27:

De-*A,B*-23,24-dinor-22-mercaptocholan-8β-ol (**3f**).

Sodium was added in 0.5-g portions to a stirred solution of De-*A,B*-24-phenyl-23-thiacholan-8β-ol (**3c**, 9.35 g) in 50 mL of dry THF and 250 mL of liquid NH_3 at -33 °C under Ar, until the blue color persisted (3.5 g Na added). The mixture was quenched *carefully* with solid NH_4Cl, and the excess NH_3 was allowed to evaporate. The residue was dissolved in ether and water, the mixture was acidified to pH 2 with 1M HCl, and partitioned between ether and water. The ethereal solution was washed with brine, dried ($MgSO_4$), filtered and concentrated to give 6.75 g of an oil.

NMR ($CDCl_3$) δ 0.94 (s, 3H), 0.99 (d, 3H), 1.0-2.0 (m, 15H), 2.5 (ABX, 2H), 4.08 (br s,1H).

Example 28:

De-*A,B*-23-thiacholestan-8β,25-diol (**3g**).

$NaOCH_3$ (2.4 mL of a 25% solution in CH_3OH) was added to a stirred solution of De-*A,B*-23,24-dinor-22-mercaptocholan-8β-ol (**3f**, 2.25 g) in 15 mL of CH_3OH under Ar. Isobutylene oxide (1.49 g) was added and the solution was heated to reflux for 2 h, then cooled to 24 °C over 15 h. The mixture was poured into water, extracted with ether and ethyl acetate and the organic extracts washed with water

(to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica (25%→50% EtOAc-hexane) to give 2.47 g of a viscous oil.

NMR ($CDCl_3$) δ 0.95(s, 3H), 1.06 (d, 3H), 1.27 (s, 6H), 1.0-2.1 (m, 15H), 2.54 (ABX, 2H), 2.63 (br s, 2H), 4.08, (1 H).

Example 29:

De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (**3h**).

4-Bromophenyl isocyanate (6.35 g) was added to a stirred solution of tosylate **3b** (9.40 g) in 50 mL of dry pyridine under Ar. After 2.5 h, 5 mL of water was added and stirring continued for 0.5 h. The mixture was diluted with ether and washed with water, 1M H_2SO_4, water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was recrystallized from ethanol to give 10.7 g of a white solid, m.p. 159-161 °C.

Anal. Calcd:	C, 57.44;	H, 6.07;	N, 2.48;	S, 5.68.
Found:	C, 57.52;	H, 6.12;	N, 2.47;	S, 5.73.

Example 30:

De-*A,B*-23,24-dinor-22-mercaptocholan-8β-ol-8β-(4-bromophenyl) carbamate (**3j**).

Potassium thiolacetate (1.75 g) was added to a stirred solution of De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (**3h**, 4.32 g) in 13 mL of dry DMF under Ar. After 70 min, the mixture was diluted with ether and ethyl acetate, washed with water (3 times), brine, dried ($MgSO_4$), filtered and concentrated, giving 3.58 g of a yellow foam. This material was dissolved in 40 mL of absolute EtOH and 20 mL of dry THF, and the solution was deoxygenated by sparging with argon. A solution of 0.85 g of NaOH in 8 mL of water was added. After 5 min, the mixture was poured into sat. KH_2PO_4, extracted with ether, and the ethereal solution dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica (10% EtOAc-hexane) to give 2.1 g of compound **3j** as a foam.

NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.03 (d, 3H), 1.1-2.1 (m, 13H), 2.50 (ABX, 2H), 5.15 (br s, 1H), 6.49 (br s, 1H), 7.35 (AB, 4H).

Example 31:

3-bromo-(2,2-dimethyl)propyl benzoate.

N-Bromosuccinimide (20.7 g) was added to a stirred solution of 5,5-dimethyl-2-phenyl-1,3-dioxane (19.2 g) in 200 mL of CCl_4 containing 8.5 g of $BaCO_3$ in suspension. The mixture was heated to reflux under Ar for 2.2 h, then cooled to 24 °C over 15 h, filtered and concentrated. The residue was partitioned between ether and water, and the ethereal solution was washed with brine, dried ($MgSO_4$), filtered and concentrated to give 24.8 g of a yellow oil which was stored in the dark at 0 °C under Ar.

NMR ($CDCl_3$) δ 1.16 (s, 6H), 3.45 (s, 2H), 4.20 (s, 2H), 7.5 (m, 3H), 8.04 (dd, 2H).

Example 32:

De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-8β-(4-bromophenyl) carbamate (**3k**).

Potassium *tert*-butoxide (0.32 g) was added to a stirred solution of De-*A,B*-23,24-dinor-22-mercaptocholan-8β-ol-8β-(4-bromophenyl) carbamate (**3j**, 1.03 g) in 5.0 mL of dry DMSO under Ar. After 1 min, 3-bromo-(2,2-dimethyl)propyl benzoate (1.23 g) was added via syringe. The mixture was stirred for 2 h, then diluted with ether, washed with water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica (10% EtOAc-hexane) to give 0.82 g of a foam.

NMR ($CDCl_3$) δ 0.85 (s, 3H), 1.04 (d, 3H), 1.10 (s, 6H), 1.0-2.1 (m, 13H), 2.45 (ABX, 2H), 2.60 (s, 2H), 4.16 (s, 2H), 5.12 (br s, 1H), 6.5 (s, 1H), 7.35 (AB, 4H), 7.4-7.6 (m, 3H), 8.04 (dd, 2H).

Example 33:

De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate (**3m**).

3-Chloroperoxybenzoic acid (0.35 g) was added in portions to a stirred solution of De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-8β-(4-bromophenyl) carbamate (**3k**, 0.41 g) in 16 mL of CH_2Cl_2, keeping T≤ 40 °C. After stirring at 24 °C for 15 h, the mixture was diluted with EtOAc, washed with 1M NaOH (twice), water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was

triturated with hexane containing 2-5% ether to give (after cooling to 0 °C) 0.36 g of a white solid, m.p. 75-78 °C.

Anal. Calcd:	C, 59.25;	H, 6.53;	N, 2.16;	S, 4.94.
Found:	C, 59.30;	H, 6.55;	N, 2.12;	S, 5.03.

Example 34:

De-*A,B*-23,24-dinor-22-(2-(5-methyl-1,3,4-thiadiazolyl)thio)cholan-8β-ol-(4-bromophenyl) carbamate (**3n**).

A stirred solution of 2-mercapto-5-methyl-1,3,4-thiadiazole (0.27 g), N,N-diisopropylethylamine (0.35 mL), and De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (**3h**, 0.57 g) in 2.0 mL of dry CH_3CN was heated to reflux under Ar for 20 min. The cooled mixture was diluted with EtOAc, washed with water, 1M HCl, water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was recrystallized from ether-hexane to give 0.28 g of a pale yellow solid, m.p. 145-149 °C.

Anal. Calcd:	C, 52.66;	H, 5.77;	N, 8.01.
Found:	C, 52.77;	H, 5.78;	N, 7.95.

Example 35:

De-*A,B*-23,24-dinor-8β-(4-bromophenylcarbamoyloxy)-22-(N,N-dimethyl-N-(2-hydroxy)ethyl)cholanammonium p-toluenesulfonate (**3p**).

A stirred solution of (N,N-dimethylamino)ethanol (2.5 mL) and De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (**3h**, 0.57 g) in 5.0 mL of absolute EtOH was heated to reflux under Ar for 6 h. The cooled mixture was partitioned between ether and water. The aqueous solution was concentrated, dried azeotropically with toluene (twice) followed by EtOH (twice) and the residue was triturated with ether to give 0.38 g of a foam.

NMR (DMSO-d_6) δ 0.98 (s, 3H), 1.09 (d, 3H), 1.1-2.1 (m, 13H), 2.27 (s, 3H), 3.05 (s, 6H), 3.4 (m, 4H), 3.8 (br s, 2H), 5.03 (br s, 1H), 5.3 (br s, 1H, exchanges), 7.3 (AB, 4H), 7.45 (s, 4H), 9.52 (s, 1H, exchanges).

Example 36:

De-*A,B*-25-methyl-23-azacholestan-8β-26-diol-8β-(4-bromophenyl) carbamate (**3q**).

A stirred solution of 3-amino-2,2-dimethyl-1-propanol (1.0 g) and De-*A,B*-23,24-dinor-22-(tosyloxy)cholan-8β-ol-(4-bromophenyl) carbamate (**3h**, 0.80 g) in 4.5 mL of dry 1,2-dimethoxyethane was heated to reflux under Ar for 6 h. The cooled mixture was diluted with EtOAc, washed with water (3 times), brine, dried ($MgSO_4$) filtered and concentrated to give 0.76 g of a foam.

NMR (DMSO-d_6) δ 0.75 (d, 3H), 0.77 (s, 3H), 0.79 (s, 3H), 0.91 (s, 3H), 1.0-2.5 (m, 18H), 3.16 (s, 2H), 5.02 (br s, 1H), 7.45 (s, 4H), 9.48 (s, 1H, exchanges).

Example 37:

De-*A,B*-23,24-dinor-8β-hydroxycholan-22-carboxylic acid (**3s**).

A stirred suspension of nitrile **3r** (6.57 g) and 6.7 g of KOH pellets in 80 mL of ethylene glycol was heated to 160 °C under Ar for 17 h. The base-soluble product was isolated giving 6.15 g ofa solid. A sample was recrystallized from n-BuCl: m.p. 129.5-131 °C.

Anal. Calcd: C, 69.96; H, 10.07

Found: C, 69.86; H, 10.13.

Example 38:

De-*A,B*-23,24-dinor-8β-hydroxycholan-22-(N-methyl-N-methoxy)carboxamide (**3t**).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (1.15 g) was added to a stirred solution of acid **3s** (0.95 g), N,N-diisopropylethylamine (1.05 mL) and N,O-dimethylhydroxylamine hydrochloride (0.59 g) in CH_3CN (2.0 mL) and CH_2Cl_2 (2.0 mL) under Ar. After 16 h, the mixture was diluted with EtOAc, extracted with 1M H_2SO_4, water (twice), brine, dried ($MgSO_4$), filtered and concentrated. The residue was crystallized (hexane - *n*-BuCl) to give 0.45 g of white crystals, m.p. 91-94 °C.

Anal. Calcd: C, 67.81; H, 10.31; N, 4.94.

Found: C, 67.89; H, 10.35; N, 4.90.

Example 39:

De-*A,B*-23,24-dinor-8β-hydroxycholan-22-(N-(2,2-dimethyl-3-hydroxy)propyl) carboxamide (**3u**).

1-Ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (0.30 g) was added to a stirred solution of acid **3s** (0.26 g) and 3-amino-2,2-dimethyl-1-propanol (0.15 g) in 1.0 mL of dry CH_3CN and 1.0 mL of dry CH_2Cl_2 under Ar. After 2 h, the mixture was diluted with EtOAc, washed with water, 1M H_2SO_4 (to pH 1), water (to pH 7), brine, dried ($MgSO_4$), filtered and concentrated. The residue was recrystallized from *n*-BuCl-EtOAc to give 0.22 g of white crystals, m.p. 172.5-175 °C.

Anal. Calcd:	C, 70.11; H, 10.84; N, 4.30.
Found:	C, 70.12; H, 10.85; N, 4.23.

Example 40:

De-*A,B*-23,24-dinor-22-(tosyloxy)-8β-(*tert*-butoxy)cholane (**3v**).

Isobutylene (40 mL) was condensed into a stirred, cooled (-78°C) solution of tosylate **3b** (3.66 g) in 25 mL of dry CH_2Cl_2 under Ar. Phosphoric acid (0.25 mL, dried with P_2O_5) was added, followed by 0.40 mL of BF_3 etherate. The solution was stirred overnight while warming to 24 °C and the excess isobutylene was allowed to evaporate through a drying tube. The solution was poured into 2M NH_4OH, extracted with ether, and the organic extracts washed with water (to pH 9), brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica (20% ether-hexane) to give 3.63 g of a viscous oil.

NMR ($CDCl_3$) δ 0.82 (s, 3H), 0.94 (d, 3H), 1.09 (s, 9H), 0.9-1.9 (m, 13H), 3.74 (br s, 1H), 3.9 (ABX, 2H), 7.35 (d, 2H), 7.8 (d, 2H).

Example 41:

Diisopropyl De-*A,B*-23,24-dinor-8β-*tert*-butoxycholan-22-phosphonate (**3x**).

(A) A solution of NaI (2.7 g) and De-*A,B*-23,24-dinor-22-(tosyloxy)-8β-(*tert*-butoxy)cholane (**3v**, 3.62 g) in 40 mL of 2-butanone was heated to reflux under Ar for 45 min, then cooled to 24 °C for 15 h. The mixture was diluted with ether, washed with water, 2M $Na_2S_2O_3$, water and brine, dried ($MgSO_4$), filtered and

concentrated to give 3.10 g of De-*A,B*-23,24-dinor-22-iodo-8β-(*tert*-butoxy)cholane (**3w**), m.p. 84-89 °C. The analytical sample, m.p. 89-91 °C, was secured by recrystallization from methanol.

Anal. Calcd: C, 53.97; H, 8.26.

Found: C, 54.08; H, 8.27.

(B) A solution of **3w** (2.85 g) and triisopropyl phosphite (21 mL) was stirred and heated to 150 °C under Ar for 1.5 h. The excess triisopropyl phosphite was removed by rotary evaporation (100 °C, ~1 mmHg) and the residue was purified by chromatography on silica (25% EtOAc-hexane) to give 2.65 g of **3x** as an oil.

NMR ($CDCl_3$) δ 0.89 (s, 3H), 1.10 (s, 9H), 1.12 (d, 3H), 1.31 (dd, 12H); 1.0 - 2.0 (m, 15H), 3.75 (br s, 1H), 4.7 (m, 2H). NMR (^{31}P, $CDCl_3$) δ 30.52.

Example 42:

De-*A,B*-8β-(benzyloxy)-23-oxocholestan-25-ol (**3z**).

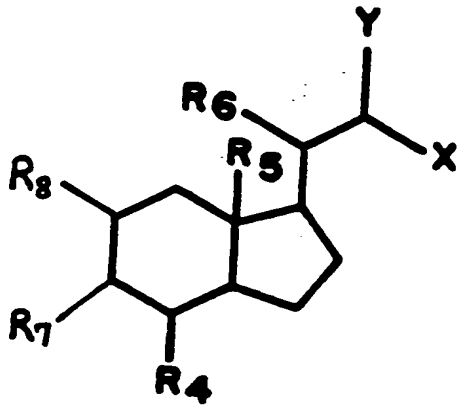
Lithium wire (1% Na) (0.21 g) was added in 0.2-cm portions to a stirred, ice-cooled solution of 4,4'-di-*t*-butylbiphenyl (8.5 g) in 90 mL of *anhydrous* THF under Ar. After stirring vigorously for 5.5 h, the deep blue-green solution was cooled to -70 °C. Isobutylene oxide (1.35 g) was added via syringe, keeping T ≤-65 °C. After 6 min, a solution of De-*A,B*-23,24-dinor-8β-(benzyloxy)cholan-22-carboxaldehyde (**3y**, 2.41 g) in 10 mL of anhydrous THF was added rapidly. The stirred mixture was allowed to warm to 8 °C over 4 h, and was then quenched with sat. KH_2PO_4 and stirred for 15 h. The phases were separated and the aqueous solution was extracted with ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica to give 2.14 g of a viscous oil. Pyridinium chlorochromate (PCC) (0.85 g) was added to a stirred solution of 0.60 g of this oil in 25 mL of dry CH_2Cl_2. After 3 h, a 0.89-g portion of PCC was added, and stirring was continued for 15 h. The mixture was eluted through Florisil with ether, and the concentrated eluate was purified by chromatography on silica (25% EtOAc-hexane) to give 0.36 g of the title compound as an oil.

NMR (DMSO-d_6) δ 0.81 (d, 3H), 0.90 (s, 3H), 1.12 (s, 6H), 1.2-2.0 (m, 13H), 2.3 (ABX, 2H), 2.45 (m, 2H), 3.63 (br s, 1H), 4.4 (AB, 2H), 4.60 (s, 1H), exchanges), 7.30 (s, 5H)

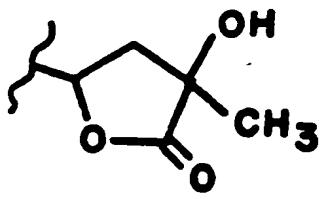
We Claim:

1. Use of a pharmaceutically effective amount of a substituted hydrindane or a pharmaceutically acceptable salt or ester of a substituted hydrindane for controlling neovascularization in warm blooded animals.

2. The use of Claim 1 wherein the substituted hydrindane has the following structure



where X is OH, OR_1, OR_2, $OS(O)_2R_3$, $ON=CHR_1$, $ON=CR_1R_1$, CN, R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_1$, $C(OR_1)R_1R_1$, $C(OR_2)R_1R_1$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, $S(=O)_nH$, $S(=O)_nR_1$, SR_2, $P(=O)R_1R_1$, $P(=O)(OH)_2$, $P(=O)(OH)(OR_1)$, $P(=O)(OR_1)(OR_1)$, $P(=O)(OH)(NH_2)$, $P(=O)(OR_1)(NH_2)$, $P(=O)(OH)(NHR_1)$, $P(=O)(OH)(NR_1R_1)$, $P(=O)(OR_1)(NHR_1)$ $P(=O)(OR_1)(NR_1R_1)$, NH_2, NHR_1, NHR_2, NR_1R_1, NR_1R_2, NHOH, $N(OH)R_1$, $N(OH)R_2$, $NH(OR_1)$, $NH(OR_2)$, $N(OR_1)R_2$, $N(OR_2)R_1$, $N(OR_2)R_2$, $N(OR_1)R_1$, $^{\oplus}S(R_1)(R_1)\ Q^{\ominus}$, $^{\oplus}N(R_1)(R_1)(R_1)\ Q^{\ominus}$ wherein $Q^{\ominus}$ is a halide, sulfonate, or carboxylate anion; $C(=O)R_1$, $C(=O)R_2$, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$, $C(=O)N(OH)R_1$, $C(=O)N(OR_1)R_1$, $C(=O)N(OR_2)R_1$; or



n = 0, 1 or 2;

R_1 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR_3, or 6 OR_2; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C_1-C_6 alkyl groups;

R_2 is C(=O)H, $C(=O)R_1$, $C(=O)OR_1$, C(=O)OH, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$;

R_3 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

R_4 is H, (=O), OR_2, OR_1, OH, =NOH, $=NOR_1$, $=NOR_2$;

R_5 and R_6 are independently H, CH_3 or CH_2CH_3;

Y is H, OH, OR_1, OR_2 or (=0), with the proviso that if Y is OH, then X is R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, and if Y is (=O) then X is R_1, R_2, $CH(OH)R_2$, $CH(OR_1)R_2$, $CH(OR_2)R_2$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, NH_2, NHR_1, NR_1R_1, NHOH, $N(OH)R_1$, $NH(OR_1)$, $NH(OR_2)_2$, $N(OR_1)R_1$, or $N(OR_2)R_1$; and

R_7 and R_8 are independently H or C_1 to C_6 alkyl, branched alkyl, hydroxyalkyl, optionally unsaturated; or R_7 and R_8 together form a double bond.

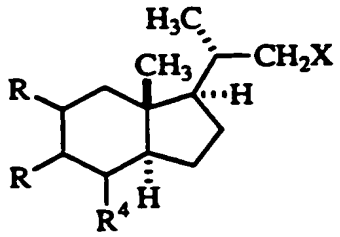
3. Use according to Claim 1 wherein the concentration of substituted hydrindane being administered is from 0.0001 to 1 weight percent.

4. Use according to Claim 1 wherein the amount of substituted hydrindane being administered is from 1 - 2000 mg.

5. Use of a pharmaceutically effective amount of a substituted hydrindane selected from the group consisting of De-*A*,*B*-26-(benzoyloxy)-25-

methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, De-*A,B*-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, and De-*A,B*-23-thiacholestan-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate.

6. A substituted hydrindane having the formula



where X is $C(OH)R_1R_1$, $C(OR_1)R_1R_1$, $C(OR_2)R_1R_1$, $C(OH)R_1R_2$, $C(OR_1)R_1R_2$, $C(OR_2)R_1R_2$, $C(OH)R_2R_2$, $C(OR_1)R_2R_2$, $C(OR_2)R_2R_2$, $S(=O)_nH$, $S(=O)_nR_1$, SR_2, $P(=O)R_1R_1$, $P(=O)(OH)_2$, $P(=O)(OH)(OR_1)$, $P(=O)(OR_1)(OR_1)$, $P(=O)(OH)(NH_2)$, $P(=O)(OR_1)(NH_2)$, $P(=O)(OH)(NHR_1)$, $P(=O)(OH)(NR_1R_1)$, $P(=O)(OR_1)(NHR_1)$ $P(=O)(OR_1)(NR_1R_1)$, NH_2, NHR_1, NHR_2, NR_1R_1, NR_1R_2, NHOH, $N(OH)R_1$, $N(OH)R_2$, $NH(OR_1)$, $NH(OR_2)$, $N(OR_1)R_2$, $N(OR_2)R_1$, $N(OR_2)R_2$, $N(OR_1)R_1$, $^{\oplus}S(R_1)(R_1)$ $Q^{\ominus}$, $^{\oplus}N(R_1)(R_1)(R_1)$ $Q^{\ominus}$ wherein $Q^{\ominus}$ is a halide, sulfonate, or carboxylate anion; $C(=O)R_1$, $C(=O)R_2$, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$, $C(=O)N(OH)R_1$, $C(=O)N(OR_1)R_1$, $C(=O)N(OR_2)R_1$;

n = 0, 1 or 2;

R_1 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl, optionally unsaturated and/or substituted with up to 6 OH, 6 OR_3, or 6 OR_2; or imidazolyl, triazolyl, thiadiazolyl, oxadiazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, or pyridyl, optionally substituted with up to three halogen or C_1 - C_6 alkyl groups;

R_2 is $C(=O)H$, $C(=O)R_1$, $C(=O)OR_1$, $C(=O)OH$, $C(=O)NH_2$, $C(=O)NHR_1$, $C(=O)NR_1R_1$;

R_3 is aryl, haloaryl, C_1 - C_{10} alkyl, branched alkyl, cycloalkyl, aralkyl, carboxyalkyl or haloalkyl optionally unsaturated and/or substituted with up to 6 OH;

R_4 is H, OR_2, OR_1, OH, =NOH, $=NOR_1$, $=NOR_2$; and provided that if X is $S(O)_2$(optionally substitued phenyl) then $R_4 \neq$ OH, or (=O); and

R_7 and R_8 are H or together are optionally a double bond;

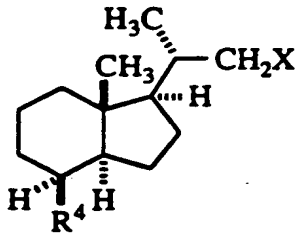
and wherein aryl denotes phenyl, naphthyl, furyl, thienyl, pyridyl, benzofuryl, indolyl, benzothienyl, quinolyl or isoquinolyl;

R_1R_1 attached to the same C, S, P or N atom can form a ring of from 3 through 7 members; and

for those substituents containing more than one R_1, R_2, or R_3, each R_1, R_2, or R_3 may be the same or different;

or a pharmaceutically acceptable salt or ester thereof.

7. A substituted hydrindane according to Claim 6 wherein the hydrindane has the formula



8. A substituted hydrindane according to Claim 7 wherein the hydrindane is selected from the group consisting of De-*A,B*-26-(benzoyloxy)-25-methyl-23-thiacholestan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, De-*A,B*-24-phenyl-23-thiacholan-8β-ol-23-dioxide-8β-(4-bromophenyl) carbamate, and De-*A,B*-23-thiacholestan-8β,25-diol-23-dioxide-8β,25-bis(4-bromophenyl) carbamate.

9. A process for preparing 3-bromo-(2,2-dimethyl)propyl benzoate which comprises the step of

reacting 5,5-dimethyl-2-phenyl-1,3-dioxane with N-bromosuccinimide in an inert solvent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/07759

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/325 A 61 K 31/045 A 61 K 31/16
A 61 K 31/19 C 07 C 323/52 C 07 C 317/18 C 07 C 309/73

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
D,A	EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 178, no. 2 , 20 March 1990 Amsterdam, NL, pages 247 - 250 T. OIKAWA, ET AL.: 'Inhibition of angiogenesis by vitamin D3 analogues' cited in the application see the whole document	1
A	EP,A,0230600 (TEVA PHARMACEUTICAL INDUSTRIES) 5 August 1987 see compounds II, IX; examples 1, 2	6
A	JOURNAL OF ORGANIC CHEMISTRY, vol. 50, no. 14 , 12 July 1985 Washington, DC, US, pages 2598 - 2600 W.S. JOHNSON, ET AL.: 'A highly selective route to calcitriol lactone' see compounds 9, 10, 15, 16	6

-/-

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02-11-1993	-7. 02. 94
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	R. English

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0115314 (HOFFMANN-LA ROCHE) 8 August 1984 see compounds VII, X; examples 6, 8	6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/07759

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5 are directed to methods of treatment of the human or animal body (Rule 39.1(iv)PCT), the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see Form PCT/ISA/206 dated 06/12/93.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5(part.), 6-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9307759 SA 78350

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/02/94
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0230600	05-08-87	AU-B-	590644	09-11-89
		AU-A-	6601086	23-07-87
		JP-C-	1739039	26-02-93
		JP-B-	4024346	24-04-92
		JP-A-	62169762	25-07-87
		JP-A-	5004962	14-01-93
		US-A-	4758382	19-07-88
EP-A- 0115314	08-08-84	DE-A-	3471928	14-07-88
		JP-A-	59141529	14-08-84
		US-A-	4594432	10-06-86

EPO FORM P0479